

**REMARKS**

Applicants respectfully submit that no prohibited new matter has been introduced by the foregoing amendments. Claims 55-91 are pending before the Examiner for examination. Claims 90 and 91 have been withdrawn as being directed to a non-elected invention. Claims 55, 58-68, 70, 71, 77, 81, 86 and 88 have been amended. Support for the amended claims can be found throughout the specification and in the original claims. Specifically, support for amended claims 55, 86 and 88 can be found on page 40, line 29, through page 42, line 14 (method of predicting a toxic effect of a test compound or hepatotoxicity by comparing one or more gene expression levels in a toxin-exposed sample to a database comprising quantitative gene expression information from liver samples exposed to the test compound and to the excipient in which that compound is prepared). Support for amended claim 62 can be found on page 18, lines 6-18; on page 40, lines 12-28; and in Table 3 (use of the genes and expression levels in Tables 1-3 to predict a toxic effect or hepatotoxicity; for each gene, the database contains mean values for toxicity group and non-toxicity group samples; group means and standard deviations for each gene in toxicity group samples in each pathology group, respectively). Amended claim 70 is supported on page 39, lines 16-22 (preparation of cDNA from liver cell or tissue samples), and amended claim 77 is supported on page 36, lines 4-8, and on page 40, lines 12-28 (database comprises gene expression levels from toxin-exposed liver samples and control liver samples exposed to the excipient in which the toxin is prepared).

The Office Action dated May 2, 2003 has been carefully reviewed and the following response is made in response thereto. In view of the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

**I. Summary of the Office Action**

1. Claims 90 and 91 have been withdrawn by the Examiner without prejudice towards further prosecution, and Applicants election of alpha-naphthylisothiocyanate (ANIT) as the toxin and liver as the tissue have been acknowledged.

2. The Office Action objected to the specification because it contained a hyperlink or

other form of browser-executable code between page 32, line 31, and page 33, line 6.

3. The Office Action objected to the Information Disclosure Statement filed on October 11, 2001 (paper no. 3) because the foreign patent documents are not in the instant application.

4. The Office Action rejected claims 55, 86 and 88, and their dependent claims 56-85, 87 and 89, under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention.

5. The Office Action rejected claims 55-60, 62-70, 72-76, 78, 79, 81 and 84-88 under 35 U.S.C. §103(a) as being unpatentable over Friend et al. (US 6,218,122) taken with Cunningham et al. (US 6,372,431).

## **II. Response to the Office Action**

### Objection to the hyperlink or browser-executable code on pages 32 and 33

The Office Action alleges that the disclosure contains an embedded hyperlink and/or other form of browser-executable code (page 32, lines 31-32, to page 33, lines 1-6). Although Internet addresses of external databases are disclosed to illustrate an embodiment of the invention, Applicants confirm that no functioning hyperlinks or browser-executable codes exist within the specification. These Internet addresses have been typed as text only. Thus, Applicants respectfully request that this objection be withdrawn.

### Objection to the Information Disclosure Statement filed on October 11, 2001

The Office Action alleges that the foreign patent documents filed in the Information Disclosure Statement (IDS) of October 11, 2001 have been misplaced by the Office. Accordingly, a copy of this IDS, including copies of the references cited therein and a copy of the receipt postcard from that filing, are submitted concurrently with this response. Because Applicants are providing copies of the foreign patents cited on October 11, 2001 to the Examiner, Applicants respectfully request that this objection be withdrawn.

### Rejection of claims 55-89 under 35 U.S.C. §112, second paragraph

The Office Action alleges that claims 55, 86 and 88, along with their dependent claims

56-85, 87 and 89, are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Purportedly, claims 55, 86 and 88 have been regarded as vague and indefinite because the steps of the claims comprise preparing and comparing gene expression profiles while the preamble recites a method of predicting a toxic effect or a method of predicting hepatotoxicity. Respectfully, claims 55, 86 and 88 as amended are not indefinite or unclear. These claims recite methods of predicting at least one toxic effect (claim 55) or a method of predicting hepatotoxicity (claims 86 and 88) of a test compound in which the method comprises the step of preparing a gene expression profile from a liver sample exposed to the test compound and the step of comparing that gene expression profile to gene expression levels in a database, in which the database contains gene expression levels from liver samples exposed to the test compound and control gene expression levels from liver samples exposed to the vehicle in which the test compound was prepared. A toxic effect, or hepatotoxicity, can be determined by analysis of the comparative gene expression levels. Thus, the methods claimed are clearly recited in the preambles and the steps comprising the methods are clearly recited in steps (a) and (b) of claims 55, 86 and 88.

The Office Action also alleges that the phrase “comparing the gene expression profile to a database” in step (b) of claims 55, 86 and 88 causes these claims to be vague and indefinite and that the step of comparing is unclear because it is uncertain what is being compared in step (b). Respectfully, it is clear in step (b) of amended claims 55, 86 and 88 that the gene expression profiles obtained in step (a) are compared to gene expression levels from test compound-exposed and excipient-exposed liver samples stored in the database. Thus, all the limitations of claims 55, 86 and 88 as amended are clear and definite, and Applicants respectfully request that the rejections of claims 55-89 under 35 U.S.C. §112, second paragraph be withdrawn.

Specific to claims 58-61, the Office Action alleges that the term “that’s” causes the claims to be vague and indefinite. In claims 58-61, the term “that’s” has been amended to “whose.” Accordingly, Applicants request that this rejection of these claims be withdrawn.

Specific to claims 61 and 71, the Office Action alleges that the phrase “protein adduct former” causes the claims to be vague and indefinite. Respectfully, protein adduct formation is mentioned in the specification on page 15, lines 23-25, and on page 17, lines 27-30. Therefore,

the recited phrase is disclosed in the specification. Nevertheless, claim 61 has been amended to recite “a toxin that forms protein adducts,” and claim 71 has been amended to recite “liver damage induced by compounds that form protein adducts.” Accordingly, Applicants request that this rejection of these claims be withdrawn.

Specific to claim 76, the Office Action alleges that the phrase “external” database causes the claim to be vague and indefinite. External databases are discussed in the specification on pages 32 and 33 (as noted above under the objection to a hyperlink or browser-executable code) and examples of external databases are given. Thus, it is clear that the external databases used in the invention are external to the database comparing quantitative gene expression information referred to in step (b) of claim 55 and, accordingly, Applicants request that this rejection of this claim be withdrawn.

Specific to claim 81, the Office Action alleges that the term “measures” causes the claim to be vague and indefinite. In claim 81, “measures” has been amended to “quantifies,” as reflected in the LDA score for each gene listed in Table 3 of the specification. The LDA score for a particular gene is an indication of its ability to predict a toxic effect or to predict hepatotoxicity. Thus, as amended, claim 81 is not vague or indefinite, and Applicants request that this rejection of this claim be withdrawn.

Rejection of claims 55-60, 62-70, 72-76, 78, 79, 81, and 84-88 under 35 U.S.C. §103(a)

The Office Action alleges that claims 55-60, 62-70, 72-76, 78, 79, 81, and 84-88 are unpatentable over Friend *et al.* (U.S. Patent No. 6,218,122 B1) taken with Cunningham *et al.* (U.S. Patent No. 6,372,431 B1). Applicants traverse this rejection and submit that the claims as amended are not obvious in view of this combination of references.

Respectfully, Friend *et al.* discloses a database of perturbation levels of cellular constituents of yeast cells achieved by disrupting the SUN2 gene (Figures 1 and 2 and column 10 line 15, through column 11, line 60). Friend *et al.* does not disclose or suggest a database of animal liver gene expression levels containing toxin-exposed and control excipient-exposed samples that can be used to predict a toxic effect of a test compound or hepatotoxicity resulting from exposure to a test compound. Additionally, the cited reference does not disclose comparing

gene expression levels, or a profile of gene expression levels, obtained from a sample exposed to a test compound to control excipient-exposed samples, or a profile of control samples, to predict a toxic effect of a test compound or hepatotoxicity resulting from exposure to a test compound. The reference also provides no guidance for developing the database of the methods of the instant invention or for predicting toxicity according to the methods of the instant invention.

Cunningham *et al.* discloses exposing rats to toxins and examining the effects on their livers, but the effects are studied by measuring the expression levels of 16 unidentified genes, SEQ ID NOS: 1-16 (see column 25, lines 10-17). Cunningham *et al.* does not disclose a database containing toxin-exposed and control excipient-exposed liver samples that can be used to predict a toxic effect of a test compound or hepatotoxicity resulting from exposure to a test compound. Similarly to Friend *et al.*, Cunningham *et al.* does not disclose comparing gene expression levels, or a profile of gene expression levels, obtained from a test-compound-exposed liver sample to control excipient-exposed samples, or a profile of control samples, to predict a toxic effect of a test compound or hepatotoxicity resulting from exposure to a test compound. Consequently, Cunningham *et al.* does not remedy the deficiencies of Friend *et al.*, nor do the references, alone or in combination, provide motivation for combining the teachings of the references to arrive at the instant invention (see MPEP 2143.01). The combination of these two references cannot be considered to render the claimed invention obvious, and, accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §103(a) be withdrawn.

### **Conclusion**

In view of the foregoing remarks, the Applicants respectfully request withdrawal of all outstanding rejections and early notice of allowance to that effect. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

**Except** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit